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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/782,075	02/19/2004	Sean D. Monahan	Mirus.030.16.6	4417

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EXAMINER	
CHONG, KIMBERLY	
ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 04/27/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/782,075	MONAHAN ET AL.	
	Examiner	Art Unit	
	Kimberly Chong	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 February 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1,4-10 and 12-14* is/are pending in the application.

4a) Of the above claim(s) *4* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 4-10, 12-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application/Amendment/Claims

Applicant's response filed 02/27/2006 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 11/29/2005 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

With entry of the amendment filed on 09/19/2005, claims 1 and 4-10 and 12-14 are pending in the application. Applicant has canceled claim 11.

Election/Restrictions

The withdrawal of claim 14 in the Office action filed 11/29/2005 as being distinct from the originally presented invention has been reconsidered. Claim 14 is directed to the elected invention and therefore will be examined along with claims 1, 4-10 and 12-13, which are currently under examination.

New Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 4-10 and 12-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tuschl et al. (cited on PTO form 892 filed 11/29/2005) in view of Goldsborough (cited on PTO form 892 filed 11/29/2005).

Claim 1 is drawn to a modified RNA comprising a functional group post-synthetically linked to an RNA via a labile bond wherein said functional group enhances delivery of said RNA to a mammalian cell and wherein said RNA is selected from the group consisting of siRNA and microRNA. Claims 4-5 limit claim 1 by reciting the modified RNA consists of a functional group is linked to a ribose 2'-hydroxyl RNA and wherein the function group is selected from a hydrophobic group, a membrane active compound, a cell penetrating compound, a targeting signal, an interaction modifier or a steric stabilizer. Claim 6 limits claim 4 by reciting the modified RNA is modified at a single ribose 2'-hydroxyl, more than one but not all of the ribose 2'-hydroxyls or all of the ribose 2'-hyrdoxyls. Claims 7-10 and 12-13 further limit claim 1 by reciting the modified RNA consists of a silylated RNA, an acylated RNA, an alkylated RNA, wherein the cell consists of an *in vivo* mammalian cell or an *in vitro* mammalian cell and wherein the modified RNA is more resistant to nucleases than an unmodified RNA.

Tuschl et al. disclose a 2'-hydroxyl post-synthetically modified siRNA wherein the modification comprises a functional group attached via a bond and (see page 5 last paragraph to page 6 first paragraph) wherein the functional group increases the RNA molecules stability and would therefore enhance delivery of the RNA to the mammalian

cell. The specification at page 15 discloses functional groups can mean chemical functional groups that can undergo further chemical reactions such as hydroxyl groups or amine groups. Tuschl et al. teach functional groups such as hydroxyl groups and amine groups (see page 6, lines 1-5) and teach siRNA comprising a plurality of functional groups attached to siRNA (see Figure 14). Tuschl et al. further disclose the modified RNA can be delivered via a transfection agent into mammalian cells *in vivo* or *in vitro* (see page 8, lines 1-18). Tuschl et al. does not teach the modified siRNA consists of a silylated RNA, an acylated RNA or an alkylated RNA.

Goldsborough disclose the RNA can consist of a silylated RNA (see page 25), an acylated RNA (see page 20) or an alkylated RNA (see page 21). Goldsborough disclose the modified RNA consists of a functional group attached to a ribose 2'-hydroxyl position (see page 41), the modified RNA has more than one, but not all of the ribose 2-hydroxl positions modified (see page 13) and the modified RNA are more resistant to nucleases (see Example 61). Goldsborough disclose a modified RNA molecule comprising a functional group at the 2'-hydroxyl position (see page 21) and wherein the functional groups increases the RNA molecule stability which would enhance delivery of the RNA to a mammalian cell.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate modification RNA such as silylated RNA, an acylated RNA or an alkylated RNA as taught by Goldsborough into the siRNA as taught by Tuschl et al.

One would have been motivated to incorporate modified silylated RNA, acylated RNA or alkylated RNA into siRNA because Goldsborough teach incorporating silylated RNA, acylated RNA or an alkylated RNA into a RNA molecule protects the RNA from degradation. Goldsborough teach RNA is inherently unstable and protecting RNA from degradation while maintaining the biological activity of RNA is essential for use by one of skill in the art (see pages 3-4). Goldsborough et al. teach modification of gene expression inhibitors such as an antisense molecule would have enhanced activity compared to natural nucleic acid molecules because they are more stable and able to enter the cell more readily (see page 71). As such, one would be motivated to increase the stability of a siRNA molecule to increase the potential for greater RNAi activity or prolonged activity of the siRNA molecule in a cell.

Finally, one would have a reasonable expectation of success because Goldsborough teach successful incorporation of a silylated RNA, acylated RNA or an alkylated RNA into a RNA molecule and further teach incorporation of such RNA does not affect the biological activity of the modified RNA.

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Response to Applicant's arguments

The rejection of record of claims 1 and 4 under 35 U.S.C. 102(e) as being anticipated by Tuschl et al. (US 2005/0059005) is maintained.

Applicant's arguments filed 02/27/2006 have been fully considered but are not persuasive. Applicant argues Tuschl et al. does not teach labile bonds or attachment of functional groups to RNA such that the groups can be removed without breaking other bonds in the RNA under any condition.

Applicant further argues examiner did not rely on the full definition of labile bond and refers to the specification at page 13, lines 1-6 wherein a labile bond is a bond that is selectively broken and the bond must be able to be broken without breaking other covalent bonds in the molecule.

As stated in the previous Office action filed 11/29/2005, examiner relied on the definition of a labile bond as being a bond that is a cleavable bond, as specifically defined on page 13, line 6. Moreover, a labile bond is any bond that is capable of being broken under certain conditions because the specification does not specifically define what selective conditions would break the labile bond. Applicant points to page 2, lines 15-16 to define conditions in which a bond is selectively broken. The specification at page 2, lines 15-16 disclose post-synthetically modified RNA wherein the *modifications* are labile under mammalian physiological conditions and do not disclose certain selective conditions in which a labile bond is broken.

Applicant's assertions that Tuschl et al. does not teach labile bonds or attachment of functional groups to RNA such that the groups can be removed without breaking other bonds in the RNA is not sufficient. MPEP 2112.01 states in part that "Where the claimed and prior art products are identical or substantially identical in structure or composition... a prima facie case of either anticipation or obviousness has

been established. *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1997)." Moreover, "When the PTO shows a sound basis for believing that the products of the applicant the prior art are the same, the applicant has the burden of showing that they are not." In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed.Cir. 1990)." Applicant has not shown that the bond attaching a functional group to a post-synthetically modified RNA taught by Tuschl et al. cannot be cleaved.

Therefore, because Tuschl et al. teach 2'-hydroxyl post-synthetically modified RNA wherein the modification comprises a functional group (see page 5 last paragraph to page 6 first paragraph) and wherein the functional group is linked to the RNA via a bond, Tuschl et al. anticipates claims 1, 4, 10 and 12 of the instant application.

The rejection of record of claims 1, 4, 10 and 12 under 35 U.S.C. 102(e) as being anticipated by Tuschl et al. (WO 02/44321) is maintained.

Applicant's amendment of claim 1 to limit the modified RNA to a siRNA or microRNA do no obviate the rejection because Tuschl et al. teach siRNA and therefore anticipate claim 1 and dependent claims 4, 10 and 12.

Moreover, the post-synthetically modified siRNA, comprising a functional group linked to the RNA via a bond, taught by Tuschl et al. in WO 02/44321 is the same nucleic acid molecule taught by Tuschl et al. in US 2005/0059005 in that the post-synthetically modified siRNA comprises a functional group linked to the RNA by a bond, however Applicant does not argue that the bond in the RNA taught by Tuschl et al. (WO 02/44321) is not labile.

Therefore, Tuschl et al. (WO 02/44321) anticipates claims 1, 4, 10 and 12 of the instant application.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly Chong whose telephone number is 571-272-3111. The examiner can normally be reached Monday thru Friday between 7-4 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached at 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Kimberly Chong
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1635